



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application : John L. Neumeyer et al.
Serial No. : 07/841,617
Filed : February 25, 1992
For : AN IODINATED NEUROPROBE FOR MAPPING
MONOAMINE REUPTAKE SITES
Examiner : M. Zmurko
Attorney's Docket : RBI-101XX

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GROUP 220

Group Art Unit: 2203

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By

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RESPONSE

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The Official Action mailed October 21, 1992, has been reviewed.

Reconsideration of the rejections is requested.

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Claims 1-45 remain in prosecution. Claims 1-45 have been made subject to a species restriction requirement. The species embodied in claims 1 and 7 have been elected for continued prosecution. Claims 1-12, 25, 26, and 29-36 are subject to a further restriction requirement under 35 USC §121. In response to the restriction requirement, Applicants elect to continue to prosecute the invention of group I, claims 1-12 and 29-36, drawn to a radiolabelled composition and a kit for its use.

Claims 1-12, 25, 26, 29-36 stand rejected.

The Examiner has rejected claims 1-12 under 35 USC §102(a) as being anticipated by the publication of Neumeyer et al. Neumeyer et al. disclose [¹²³I]-2β-carbomethoxy-3β-(4-iodophenyl)tropane as a high affinity SPECT radiotracer of monoamine reuptake sites in the brain.

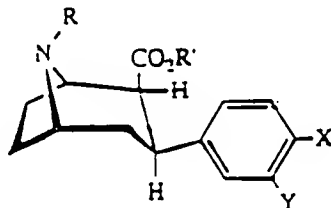
The Manual of Patent Examining Procedure §715.01(c) provides that "[w]here the applicant is one of the co-authors of a publication cited against his or her application . . . [t]he publication may be removed as a reference by filing a disclaiming affidavit or declaration of the other authors." Ex Parte Hirschler, 110 USPQ 384 (1952). The Applicants submit herewith declarations of authors cited in the Neumeyer et al. publication, Shaoyin Wang, Ronald Baldwin, Yolanda Zea-Ponce, Paul Hoffer, Mohammed Al-Tikriti, Dennis Charney, Robert Malison, and Marc Laruelle stating that each individual is not an inventor of the present invention, and that each individual's name was included in the

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Neumeyer et al. publication in order to receive credit for collaborating with the inventors. Also submitted is the declaration of Dr. Robert B. Innis, an inventor of the present invention, stating that Elzbieta Sybirska, who is also listed as an author in the Neumeyer et al. publication, worked under his direction, is not an inventor of the present invention, and is not presently available to sign a declaration to these facts. The Applicants therefore submit that the Neumeyer et al. publication may now be removed as a reference, and that this basis of rejection is overcome.

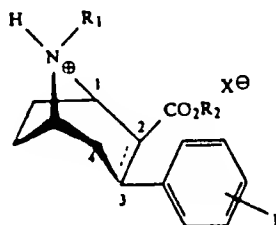
The Examiner has rejected claims 1-12 under 35 USC §102(e) as being anticipated by Carroll et al. The Applicants respectfully traverse this basis for rejection.

Anticipation requires that every element of the claim, arranged as in the claim, is identically shown by a single prior art reference. Claim 1 of the present invention recites an iodinated neuroprobe for mapping monoamine reuptake sites, the iodinated neuroprobe being of the formula:



wherein R is a monofluoroalkyl group including ⁿF where n=18 or 19; R' = a C_nH_{2n+1} group where n=0-6; X = an isotope of I; and Y = H.

By contrast, Carroll et al. claim a compound of the formula:



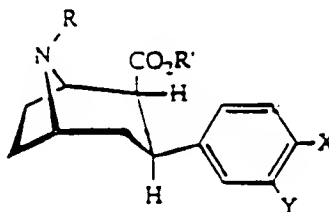
where the broken line represents an optional chemical bond and the substituents at 2 and 3 may be at any position; the iodo substituent may be at o, m, or p, or multisubstituted; R₁ is CH₃, CH₂CH=CH₂, (CH₂)_nC₆H₅ where n=1-4; R₂ is CH₃, C₂H₅, CH₃(CH₂)₃, (CH₃)CH, C₆H₅, C₆H₅CH₂, C₆H₅(CH₂)₂; X is a pharmacologically acceptable anion; and the iodo substituent is radioactive.

Therefore, Carroll et al. do not claim a monofluoroalkyl group including ¹⁸F where n=18 or 19 at the R position. The Applicants therefore submit that since the claims of Carroll et al. do not claim a monofluoroalkyl group including ¹⁸F where n=18 or 19 at the R position as claimed in the present invention, Carroll et al. cannot anticipate the presently claimed invention. Therefore, the Applicants submit the basis for rejection under §102(e) has been overcome.

The Examiner has rejected claims 1-12 and 24-25 under 35 USC §103 as unpatentable over Neumeyer et al. in view of Jacobson et al. The Examiner also has rejected claims 1-12 under 35 USC §103 as unpatentable

over Carroll et al. in view of Jacobson et al. The Applicants respectfully traverse these rejections.

As stated above claim 1 of the present invention recites an iodinated neuroprobe for mapping monoamine reuptake sites, the iodinated neuroprobe being of the formula:



wherein R is a monofluoroalkyl group including ^nF where $n=18$ or 19 ; $\text{R}' = \text{a } \text{C}_n\text{H}_{2n+1}$ group where $n=0-6$; $\text{X} = \text{an isotope of I}$; and $\text{Y} = \text{H}$.

As stated above, the Examiner's rejection based on the combination of Neumeyer et al and Jacobson et al. is not justified since Neumeyer et al. has been removed as a reference pursuant to MPEP §715.01(c). Further, even if the Neumeyer reference were available as a reference, the combination of Neumeyer et al. and Jacobson et al. would not make Applicants invention obvious.

Neumeyer et al., as the Examiner admits, does not disclose or suggest the use of a monofluoroalkyl group including ^nF where $n=18$ or 19 at the R position. Instead Neumeyer et al. discloses a methyl group or a hydrogen atom bonded to the bridge nitrogen, rather than a monofluoroalkyl group. Neumeyer et al. does not teach or suggest that

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a monofluoroalkyl group is desirable to use or even possible to synthesize.

Jacobson et al. teach that radioactive fluorine can be introduced into biologically active molecules using a p-bromomethyl benzoyl group attached to an amine. The method of attachment utilizes an N-succinimidyl-p-(bromomethyl)-benzoate intermediate which is reacted with a drug or peptide to yield a p-bromomethyl benzoyl group coupled to the amine; fluorine is then substituted for bromine (col. 2, lines 35-60 and col. 3, lines 17-28). The product of the reaction contains a new amide bond between the carbonyl group of the ester and the attacking amino group (col. 2, lines 35-60). Therefore, the halogenated group in Jacobson et al. will always be linked to the molecule through an amide bond ($X-R-CO-NR_1R_2$, see col. 2, line 60).

The present invention, by contrast, discloses a monofluoroalkyl group at the R position where the linkage between the halogenated group and the drug results in a fluorinated tertiary amine ($F-R_1-NR_2R_3$). Applicants submit first of all, that there is no motivation to combine Neumeyer et al. and Jacobson et al., since Neumeyer et al. do not teach the desirability of a monofluoroalkyl group. Further, the Applicants submit that the tertiary amine of the present invention is a chemically distinct group from the amide product of Jacobson et al. and results in different biologic responses. One skilled in the art of organic chemistry would appreciate that a monofluoroalkyl group is an alkane

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with only one fluorine atom attached, and that this group does not contain any carbonyl functionalities. Further, one skilled in the art would immediately recognize that monofluoroalkyl groups cannot be introduced to the R position of the present invention using the succinimidyl chemistry disclosed in the Jacobson et al. reference. As discussed hereinabove, the product of Jacobson et al. results in an amide group, whereas the present invention discloses a tertiary amine derivative. Therefore, the Applicants submit that in order to produce the molecule of the present invention, one skilled in the art of organic chemistry would not look to the work of Jacobson et al. to attach radioactive fluorine, and that the Jacobson et al. reference does not motivate, teach, or suggest of the Applicants' invention.

Further, the Applicants submit that the Examiner's rejection based on the combination of Carroll et al. and Jacobson et al. is not justified for reasons similar to those discussed above with respect to Neumeyer et al. That is, Carroll et al. does not disclose or suggest a monofluoroalkyl group at the R position of the present invention, and the combination of Carroll et al. and Jacobson et al. would not produce Applicants' invention.

Therefore, based on the preceding remarks, the Applicants submit that this basis for rejection is overcome, and that claims 1 is allowable as written and claims 2-12 are allowable as depending from an allowable base claim.

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The Examiner has rejected claims 24-25 under 35 USC §103 as unpatentable over Neumeyer et al. in view of Jacobson et al.

The Applicants submit that claims 24 and 25 are not drawn to the elected invention and therefore the Examiner's rejection of these claims is inappropriate.

The Examiner has rejected claims 29-36 under 35 USC §103 as being unpatentable over Carroll et al. or Neumeyer et al. in view of Nosco. The Applicants respectfully traverse this basis for rejection.

The Carroll et al. and Neumeyer et al. references have been discussed above.

Nosco discloses a method of preparing radiopharmaceutical compositions comprising complexes of technetium-99m, and a kit for preparing such compositions. In particular, Nosco discloses reacting radioactive technetium-99m in the form of a pertechnetate in the presence of a reducing agent and an optional chelator (col. 5, lines 26-30, col. 6, lines 3-28, col. 6, lines 44-45). By contrast, the kit of the present invention employs an oxidizing agent to oxidize the precursor compound in the presence of a suitable radioactive compound (page 24, lines 15-25).

The patent of Nosco does not teach or suggest a kit that employs an oxidizing agent to oxidize the precursor compound in the presence of a suitable radioactive compound. Therefore, Nosco, either alone or in combination with any other of the references of record does not teach or suggest Applicants' invention. Applicants submit that claims 29-36 are

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in condition for allowance and request that the Examiner reconsider his rejection.

Applicants submit that all claims are in condition for allowance and respectfully request reconsideration and early favorable action by the Examiner.

If the Examiner believes a telephone conference would aid in the continued prosecution of this application, the Examiner is respectfully requested to contact Applicants' representative at the telephone number listed below.

Respectfully submitted,

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